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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/741,106	12/21/2000	Michael A. Innis	12441.00003	7590

7590 10/27/2003

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/741,106	INNIS ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cov r sh et with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-27,73 and 88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-27,73 and 88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed September 23, 2003 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Priority

2. Applicant indicates the instant application is a Continuation of U. S. Patent Application 08/943,682, filed October 14, 1997, now U. S. Patent 6,174,721. However, it does not indicate 08/943,682 is a Continuation of 08/438,184, filed 05/09/1995 (abandoned), which is a Continuation of 08/286,521, filed August 5, 1994. Therefore, the priority date of August 5, 1994 is not perfected.

Status of the Claims

3. Claims 1-11, 13-27, 73 and 88 are pending.

Applicants' amendment filed September 23, 2003 is acknowledged. Applicants' response has been fully considered. Claims 1, 2, 13 and 16 have been amended. Thus, claims 1-11, 13-27, 73 and 88 are examined.

Objection Withdrawn

4. The previous objection of claims 2 and 16 is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 10 in the amendment filed September 23, 2003.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

5. The previous rejection of claims 2-13, under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 13 in the amendment filed September 23, 2003.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-11, 16-25 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U. S. Patent 6,174,721. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11, 16-25 and 73 in the instant application disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof, wherein the chimeric protein binds and inhibits factor VIIa/tissue factor complex and binds to and inhibits factor Xa. This is obvious in view of claims 1-17 in the patent which disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1

of TFPI-2 and a Kunitz-type domain 2 of TFPI, wherein chimeric protein lacks sites for N-glycosylation. Both sets of claims cite a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI. Thus, claims 1-11, 16-25 and 73 in present application and claims 1-17 in the patent are obvious variations of a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI.

7. Claims 1-11, 16-27 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U. S. Patent 5,589,359. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11, 16-27 and 73 in the instant application disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof, wherein the chimeric protein binds and inhibits factor VIIa/tissue factor complex and binds to and inhibits factor Xa. This is obvious in view of claims 1-24 in the patent which disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI. Both sets of claims cite a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI. Thus, claims 1-11, 16-27 and 73 in present application and claims 1-24 in the patent are obvious variations of a chimeric protein

comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI.

In response, applicants indicate they will consider filing a Terminal Disclaimer upon indication of allowability of the pending claims. The comment is unpersuasive. The ground of rejection remains. No allowable material can be indicated when a ground of rejection remains.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-11, 13, 16-27, 73 and 88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or, a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and a Kunitz-type domain 2 of TFPI or a mutein thereof, wherein the chimeric protein binds and inhibits factor VIIa/TF complex and factor Xa, and wherein the substitution in the mutein is defined (see page 8, line 19-page 9, line 3; page 10, line 5-12); or the chimeric protein of TFPI or TFPI-2 domains or mutein thereof as indicated in the prior art, does not reasonably provide enablement for a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or, a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and a Kunitz-type domain 2 of TFP or a mutein thereof, wherein the chimeric protein binds and inhibits factor VIIa/TF complex and factor Xa, but the structure of the mutein is not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it

is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-11, 13, 16-27, 73 and 88 encompass a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. The specification indicates the mutein of TFPI or TFPI-2 has 1-5 amino acid substitutions in the wild-type sequence, and further describes certain substitutions in the muteins, however, it does not identify most substitutions in the TFPI or TFPI-2, nor demonstrates the effects of the muteins on factor VIIa/TF and factor Xa (page 7, line 26-page 8, line 3; page 8, line 19-page 9, line 21; page 10, lines 5-12). There are no indicia that the present application enables the full scope in view of the chimeric protein comprising the muteins of TFPI or TFPI-2 as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the claims are enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the scope of the claims, the state of the prior art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the muteins of TFPI or TFPI-2 in the chimeric protein, which are not adequately described or demonstrated in the specification.

(2). The presence of working examples:

The specification has shown the mutein has the amino acid sequence of SEQ ID NO:9 (276 amino acid residues) or SEQ ID NO:19 (161 amino acid residues), where a Lys at position 36 is substituted with Arg. There are no other working examples indicating the claimed variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., WO 91/02753) indicates TFPI with certain amino acid residues such as C-terminal region deleted has TFPI activity but with no or low heparin binding activity; and Innis *et al* (U. S. Patent 5,563,123) teach chimeric proteins of TFPI or TFPI-2 domains or muteins thereof, where certain substitutions in the muteins are shown. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of the muteins and the effects of the chimeric proteins containing the muteins to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof, where the chimeric protein binds and inhibits factor VIIa/TF complex and factor Xa. The specification indicates muteins have 1-5 amino acid substitutions in the wild-type sequence, and describes certain substitutions in the muteins (e.g., the substitution at the P1 reactive site and substitutions at positions within 5 amino acids of the P1 reactive sites in Kunitz-type domains; page 7, line 26-page 8, line 3; page 8, line 19-page 9, line 21), however, it does not identify most substitutions in the TFPI or TFPI-2, nor demonstrates the inhibitory effect of

the mutein to factor VIIa/TF and factor Xa. Moreover, there are no working examples indicating various muteins except for the substitution at P1 reactive site of Kunitz-type domains, e.g., SEQ ID NO:9. Furthermore, the specification has not demonstrated the chimeric proteins containing various muteins of Kunitz-type domain 1 or 2 of TFPI or TFPI-2 have inhibitory activity against factor VIIa/TF and factor Xa. Since the specification fails to provide sufficient teachings on identities of various muteins and the effects of the chimeric proteins containing the muteins, it is necessary to have additional guidance on the muteins and to carry out further experimentation to assess the inhibitory effects of chimeric proteins containing muteins on Factor VIIa/TF/Xa.

(5). Predictability or unpredictability of the art:

The specification only identifies a specific mutien (e.g., SEQ ID NO:9 or 19) containing a substitution at the P1 reactive site, however, it does not indicate the identities of chimeric proteins containing various muteins of TFPI and TFPI-2, nor demonstrates the effects of these variants, thus, the effects of these chimeric proteins are unpredictable.

(6). Nature of the Invention

The scope of the claims includes many structural variants, however the specification has not identified these variants, nor has demonstrated the effects of the chimeric proteins containing these variants. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the inhibitory effect of the claimed invention toward Factor VII/TF and factor Xa.

In response, applicants indicate "mutein" has been defined in the specification, and the specificaiton teaches numerous examples of such muteins of TFPI and TFP-2, and these teachings bear a reasonable correlation to the scope of the recited muteins of Kunitz-type domains 1 and 2 of TFPI and TFPI-1; and claim 1 has been amended to include "the chimeric protein binds and inhibits factor VIIa/tissue factor complex and binds to and inhibits factor Xa", which excludes muteins that would render the claimed proteins non-functional; and three references (Hamamoto et al., J. Biol. Chem. 268, 8704-8710 (1993); Huang et al. J. Biol. Chem. 268, 16950-26955 (1993); Sprecher et al., PNAS 91, 3353-3357 (1994) provided by applicants) would teach the assay method to identify muteins of the recited Kunitz domains that inhibit factor VIIa/TF and factor Xa, which would fall within the scope of the claim (pages 11-13 of the response). The response has been fully considered, however, the argument is found persuasive because the specification has only described certain substitution in the muteins, while the claims include many undefined muteins, thus, the full scope of the claim is not enabled as indicated in the section above. Furthermore, the claim encompasses muteins without any structural definition, although it recites the function of the chimeric protein containing the mutein, without performing further experimentation one skilled in the art would not know how to identify a functional mutein and assess its inhibitory effects on Factor VIIa/TF and factor Xa.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-11, 13, 16-27, 73 and 88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11, 13, 16-27, 73 and 88 are indefinite because of the use of the term "TFPI" or "TFPI-2". The term "TFPI" or "TFPI-2" renders the claim indefinite, it is unclear what the term means. A fully spelled out word should be indicated in the first occurrence. Claims 2-11, 13, 16-27, 73 and 88 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-11, 13-27, 73 and 88 are rejected under 35 U.S.C. 102(b) as being anticipated by Innis *et al.* (U. S. Patent 5,563,123, Oct. 8, 1996).

Innis *et al* teach chimeric proteins (e.g., formula A-$(X_1)_a$-B-$(X_2)_b$-C or A-$[X_1$-B-$X_2]_c$-C), which are capable of binding factor VIIa/tissue factor complex and factor Xa, contain a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof (columns 8-11; claims 1, 2, 13, 16 and 88), and the flanking peptides (e.g., A or C) may contain Kunitz-type domain 3 of TFPI or TFPI-2 (claims 3, 4, 17 and 18), C-terminal tail of TFPI or TFPI-2 (claims 10, 11, 24 and 25), or amino acid sequences such as

heparin binding domain which can bind cell surface components (claims 5-9 and 19-23). The chimeric protein such as SEQ ID NO:19 can be produced in yeast cell and can further contains other protease inhibitors such as protease nexin 1 (column 16, line 50-column 17, line 8; claims 14, 15, 26 and 27). The chimeric proteins can be prepared with a pharmaceutically acceptable carrier in a pharmaceutical formulation (columns 17 and 18; claim 73).

Addition of all continuation data of the instant application to the specification would eliminate the rejection.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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October 23, 2003